

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P/2500.W00AM		FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 98/01510		International filing date (day/month/year) 26/05/1998	
Applicant MEDICAL RESEARCH COUNCIL et al.		Priority Date (day/month/year) 23/05/1997	

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☒ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application.

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title,

☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

NUCLEIC ACID BINDING POLYPEPTIDE LIBRARY

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. 1c

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

/GB 98/01510

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/10 C12N15/12
C07K14/47 A61K48/00

C07K1/04

C12N15/62

C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12Q C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ° Citation of document, with indication, where appropriate, of the relevant passages

Relevant to claim No.

P, X

M. ISALAN ET AL: "Synergy between adjacent zinc fingers in sequence-specific DNA recognition"
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,
vol. 94, 27 May 1997, pages 5617-5621,
XP002075337
WASHINGTON US
see the whole document

1-25

X

CHOO Y ET AL: "DESIGNING DNA-BINDING PROTEINS ON THE SURFACE OF FILAMENTOUS PHAGE"
CURRENT OPINION IN BIOTECHNOLOGY,
August 1995, pages 431-436, XP000652427
cited in the application
see the whole document
see page 432, column 1

1-6

Y

10-25

-/--



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

Date of the actual completion of the international search

1 September 1998

Date of mailing of the international search report

30/09/1998

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cervigni, S

INTERNATIONAL SEARCH REPORT

International Application No

/GB 98/01510

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 06166 A (MEDICAL RES COUNCIL ;CHOO YEN (SG); KLUG AARON (GB); GARCIA ISIDRO) 29 February 1996 cited in the application see the whole document see page 5-6 see page 9, paragraph 3 see page 15, paragraph 2 see figures 2,7,15; tables 1,2 -----	10-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01510

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606166 A	29-02-1996	AU 3229195 A	14-03-1996
		CA 2196419 A	29-02-1996
		EP 0781331 A	02-07-1997
		JP 10504461 T	06-05-1998

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P2500WOQ ATM		FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB98/01510	International filing date (day/month/year) 26/05/1998	Priority date (day/month/year) 23/05/1997	
International Patent Classification (IPC) or national classification and IPC C12N15/10			
Applicant MEDICAL RESEARCH COUNCIL et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14/10/1998	Date of completion of this report 9. 08. 99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Grosskopf, R Telephone No. (+49-89) 2399 8714 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/01510

I. Basis of the report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

Description, pages:

1-40 as originally filed

Claims, No.:

8-25 as originally filed

1-7 as received on 12/05/1999 with letter of 12/05/1999

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 7-25.

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/GB98/01510

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 7-25 are so unclear that no meaningful opinion could be formed (specify):

see separate sheet
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/01510

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations

see separate sheet

Ad item V:

The principle of creating a zinc finger polypeptide library wherein more than one zinc finger has been randomised is already disclosed in D1 (Current Opinion in Biotechnology (1995), pages 431-436) and possible applications thereof have been described.

Admittedly, D1 discusses the impossibility to create "full libraries of three fingers each comprehensively randomized in four positions" due to the limited capacity of the display on phages. Nevertheless the creation of libraries having more than one finger which has been randomised becomes obvious from the disclosure of D1. The creation of such a library seems to be possible with the capacities of the phage libraries which are available in the art, especially when considering merely a partial randomisation.

Therefore, the general claims 1 to 6 lack an inventive activity (Article 33.3 PCT).

Moreover, the question has to be asked whether the libraries claimed (or the set of libraries) are clearly distinguishable from e.g. reassembled libraries wherein each of the fingers has been randomized individually, since both consist of a set of "altered" polypeptides (whereas the randomisation appears to be primarily a statistical phenomenon).

Ad item III and IV:

As far as the other claims are concerned which relate to more specific embodiments, it is not possible to establish a meaningful opinion with regard to novelty and/or inventive activity for several reasons:

First, in view of the fact that the basic idea of the present application is already known, claims which relate to different but equivalent modifications therefore (i.e. to modifications of Claims 1 to 6) are no longer connected by a common inventive concept (see especially Claims 9 to 25).

This results in a set of different and independently claimed alternatives which, strictly speaking, increases the number of "quasi"-independent claims to an unreasonable number (Article 6 PCT).

The same, in principle applies with regard to claims wherein different modifications are "listed" (see e.g. Claims 7 and 8). Thus, when considering e.g. Claim 7, it is not clear whether **all** of said randomisations have to be present in the libraries or whether only some (or only one) of them must be present ("may appear").

If the first applied, the combination of all of said (selected) randomisations would not be derivable from the cited prior art.

In the second case, also with regard to these claims the objections for lack of unity apply. Moreover, in this case it must be mentioned that most of the (single) randomisations are, of course, known in the art.

Claims

1. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger and wherein each polypeptide has been at least partially randomised such
5 that the randomisation extends to cover the overlap of a single pair of zinc fingers.
2. A library according to claim 1 wherein each polypeptide comprises between three and six zinc fingers.
- 10 3. A library according to claim 1 or claim 2, wherein one and a half zinc fingers are randomised in each polypeptide.
4. A set of zinc finger polypeptide libraries which encode overlapping zinc finger polypeptides, according to any one of claims 1 to 4, wherein the polypeptides may be
15 assembled after selection to form a multifinger zinc finger polypeptide.
5. A set according to claim 4, comprising a pair of libraries encoding three-zinc finger polypeptides.
- 20 6. A library or set of libraries according to any preceding claim, wherein the randomised positions are selected from positions -1, 1, 2, 3, 5 and 6.
7. A library according to any preceding claim, wherein the randomisation of amino
25 acid residues is restricted such that the following amino acids may appear at the given positions:

Position	Possible Amino Acids
-1	R, Q, H, N, D, A, T
1	S, R, K, N
2	D, A, R, Q, H, K, S, N
3	H, N, S, T, V, A, D
5	I, T, K
6	R, Q, V, A, E, K, N, T

SOUTHAMPTON

TENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

MASCHIO, Antonio
D. Young & Co.
21 New Fetter Lane
London EC4A 1DA
ROYAUME-UNI

Receivable not ATM

Date of mailing (day/month/year)

06 October 1999 (06.10.99)

Applicant's or agent's file reference

P/2500.WOQAM

IMPORTANT NOTIFICATION

International application No.

PCT/GB98/01510

International filing date (day/month/year)

26 May 1998 (26.05.98)

1. The following indications appeared on record concerning:



the applicant



the inventor



the agent



the common representative

Name and Address

MEDICAL RESEARCH COUNCIL
20 Park Crescent
London W1N 4AL
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:



the person



the name



the address



the nationality



the residence

Name and Address

GENDAQ LIMITED
1-3 Burtonhole Lane
Mill Hill
London NW7 1AD
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:



the receiving Office



the International Searching Authority



the International Preliminary Examining Authority



the designated Offices concerned



the elected Offices concerned



other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Kari Huynh-Khuong

Telephone No.: (41-22) 838.89.38



CERTIFICATE OF INCORPORATION ON CHANGE OF NAME

Company No. 3756817

The Registrar of Companies for England and Wales hereby certifies that
ENDLOCK LIMITED

having by special resolution changed its name, is now incorporated
under the name of
GENDAQ LIMITED

Given at Companies House, Cardiff, the 24th June 1999



THE OFFICIAL SEAL OF THE
REGISTRAR OF COMPANIES



C O M P A N I E S H O U S E

PATENT ASSIGNMENT

DATE: 21 May 1999

PARTIES:

- (1) MEDICAL RESEARCH COUNCIL (a body incorporated by Royal Charter) of 20 Park Crescent, London W1N 4AL, England ("Assignor")
- (2) ENDLOCK LIMITED (Registered in England No. 3756817) whose registered office is at 90 Long Acre, London WC2E 9TT, England ("Assignee")

RECITALS:

- (A) The ASSIGNOR is the applicant in respect of the patent applications named in the Schedule to this Assignment (the "Applications") in respect of the inventions disclosed in the Applications (the "Inventions").
- (B) The parties have agreed that all the Assignor's rights in the Applications and the Inventions shall be assigned to the Assignee.

OPERATIVE TERMS:

In consideration of the sum of £1,450 paid by the Assignee to the Assignor (the receipt and sufficiency of which is hereby acknowledged) IT IS AGREED as follows:

I. Assignment

The Assignor hereby assigns to the Assignee throughout the world:

- (a) the Inventions and all right and title of the Assignor therein;
- (b) the Applications and all patent applications, patents and supplementary protection certificates which may derive or result from any of the same, including any divisionals, continuations, reissues, extensions and registrations in relation to any thereof and all and any other rights in the inventions comprised in the above (together referred to as the "Patent Rights");
- (c) the benefit of all priority dates;
- (d) its right to apply for and obtain patents, registrations or similar forms of protection in other countries in respect of the Inventions or otherwise included in or derived from the Patent Rights;
- (e) its right to make any new application(s) in respect of any parts of the subject matter of any application or specification filed in connection with the Inventions and the right to claim priority from the Applications;

- (f) its right to sue for and obtain injunctive relief, damages and all other relief in respect of any infringement or misuse (whether past present or future) of the Applications or of the rights conferred by publication of the same or of any other of the Patent Rights.

2. Validity

The Assignor has made available to the Assignee its case information concerning the current state and progress of the Applications but nothing in this Assignment shall be construed as a representation or warranty that any of the Applications will proceed to grant or that any of the Patent Rights are valid or that any exploitation of the Inventions represented by the Applications will not be an infringement of any patents or other rights not vested in the Assignor.

3. Further Assurance

The Assignor agrees at the request and expense of the Assignee to execute any further documents and do all things which the Assignee may reasonably require in order to vest in the Assignee (or the Assignee's successors in title or nominees as the case may be) the Patent Rights including the Applications and all other rights title and interests intended to be assigned transferred or granted to the Assignee hereunder and to give the Assignee the full benefit of this Assignment including doing all acts which may be necessary or desirable to record the Applications and any other Patent Rights in the name of the Assignee in any relevant register of patent rights.

4. Law

This Assignment shall be governed by and construed and take effect in accordance with English law.

IN WITNESS of which the parties have executed this Assignment on the date shown at the beginning of this Assignment.

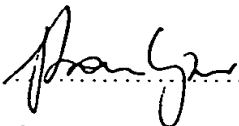
SCHEDULE

Number

PCT/GB95/01949	(granted in Australia, but pending elsewhere)
PCT/GB98/01510	
PCT/GB98/01512	
PCT/GB98/01514	
PCT/GB98/01516	
GB:980 5576.7	
GB:980 6895.0	
GB: 980 7246.5	

GB: 9824544.2 (originally GB: 9723430.6)

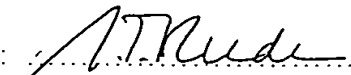
EXECUTED for and on behalf of
MEDICAL RESEARCH COUNCIL

Signature: 

Name: Graham L. Wagner
Licensing and Agreements Manager

Title:

EXECUTED for and on behalf of
ENDLOCK LIMITED

Signature: 

Name: Stephen T. Reide

Title: Director

F I N T COOPERATION TR A.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing:

26 November 1998 (26.11.98)

International application No.:

PCT/GB98/01510

Applicant's or agent's file reference:

P/2500.WOQAM

International filing date:

26 May 1998 (26.05.98)

Priority date:

23 May 1997 (23.05.97)

Applicant:

CHOO, Yen et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

14 October 1998 (14.10.98)



in a notice effecting later election filed with the International Bureau on:

2. The election



was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211, Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

P/2500.WQQAM

Box No. I TITLE OF INVENTION
Library System

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

Medical Research Council
20 Park Crescent
London
W1N 4AL
United Kingdom

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (i.e. country) of nationality:
United Kingdom

State (i.e. country) of residence:
United Kingdom

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

CHOO, Yen
C/O MRC Laboratory of Molecular Biology
Medical Research Council Centre
Hills Road
Cambridge
CB2 2QH United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:
GREECE

State (i.e. country) of residence:
United Kingdom

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MASCHIO, Antonio
D Young & Co
21 New Fetter Lane
London
EC4A 1DA
United Kingdom

Telephone No.

+44 1703 634816

Facsimile No.

+44 1703 224262

Teleprinter No.

477667 YOUNGS G

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

KLUG, Aaron
C/O MRC Laboratory of Molecular Biology
Medical Research Council Centre
Hills Road
Cambridge
CB2 2QH
United Kingdom

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:
United Kingdom

State (i.e. country) of residence:
United Kingdom

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

ISALAN, Mark
24 Shottfield Avenue
East Sheen
London
SW14 8EA
United Kingdom

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:
United Kingdom

State (i.e. country) of residence:
United Kingdom

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box*If the Supplemental Box is not used, this sheet need not be included in the request.**Use this box in the following cases:**1. If, in any of the Boxes, the space is insufficient to furnish all the information:**in particular:*

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:*
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:*
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:*
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents:*
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":*
- (vi) if there are more than three earlier applications whose priority is claimed:*

*in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;**in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below;**in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;**in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;**in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;**in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;**in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.**2. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:**in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.*CONTINUATION OF BOX IV - ADDITIONAL REPRESENTATIVES

PURVIS, William Michael Cameron
 COTTER, Ivan John
 PILCH, Adam John Michael
 CRISP, David Norman
 ROBINSON, Nigel Alexander Julian
 HARRIS, Ian Richard
 TURNER, James Arthur
 HARDING, Charles Thomas
 MALLALIEU, Catherine Louise
 PRICE, Paul Anthony King
 PRATT, Richard Wilson
 HOLMES, Miles Keeton
 HORNER, David
 NACHSHEN, Neil
 POTTER, Julian Mark

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BB Barbados | |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GW Guinea-Bissau | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> JP Japan | |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> YU Yugoslavia |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| <input checked="" type="checkbox"/> LR Liberia | |
| <input checked="" type="checkbox"/> LS Lesotho | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ CY Cyprus (in respect of the EP designation)
- ☐
- ☐

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) United Kingdom	23.05.97	9710809.6	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / epo

Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office): Date (day/month/year): Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

- 1. request : 5 sheets
- 2. description : 40 sheets
- 3. claims : 5 sheets
- 4. abstract : 1 sheets
- 5. drawings : 6 sheets

Total : 57 sheets

This international application is accompanied by the item(s) marked below:

- 1. ☐ separate signed power of attorney
- 2. ☐ copy of general power of attorney
- 3. ☐ statement explaining lack of signature
- 4. ☐ priority document(s) identified in Box No. VI as item(s):
- 5. ☐ fee calculation sheet
- 6. ☐ separate indications concerning deposited microorganisms
- 7. ☐ nucleotide and/or amino acid sequence listing (diskette)
- 8. ☐ other (specify):

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



A MASCHIO

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1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

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Date of receipt of the record copy by the International Bureau: